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Health and Environmental Effects Profile for TCAB, TCAOB and TCEB

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR TCAB, TCAOB AND TCHB

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16. ABSTRACT

The Health and Environmental Effects Profile for TCAB, TCAOB and TCHB was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for TCAB, TCAOB and TCHB.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ values for TCAB, TCAOB and TCHB are 100, 100 and none, respectively.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	2
1.3.	PRODUCTION DATA	3
1.4.	USE DATA	5
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	6
2.1.	AIR	6
2.2.	WATER	6
2.3.	SOIL	9
3.	EXPOSURE	12
4.	PHARMACOKINETICS	16
4.1.	ABSORPTION	16
4.2.	DISTRIBUTION	16
4.3.	METABOLISM	16
4.4.	EXCRETION	17
5.	EFFECTS	18
5.1.	CARCINOGENICITY	18
5.2.	MUTAGENICITY	18
5.3.	TERATOGENICITY	19
5.4.	OTHER REPRODUCTIVE EFFECTS	25
5.5.	CHRONIC TOXICITY	25
5.6.	OTHER RELEVANT INFORMATION	33
6.	AQUATIC TOXICITY	35
7.	EXISTING GUIDELINES AND STANDARDS	36
7.1.	HUMAN	36
7.2.	AQUATIC	36
8.	RISK ASSESSMENT	37
9.	REPORTABLE QUANTITIES	40
9.1.	REPORTABLE QUANTITY RANKING (RQ) BASED ON CHRONIC TOXICITY	40
9.2.	WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY	41
10.	REFERENCES	46
APPENDIX:	LITERATURE SEARCHED	58

LIST OF TABLES

No.	Title	Page
1-1	TCAB and TCAOB Contamination Levels in Anilide Herbicides and 3,4-Dichloroaniline.	4
3-1	Summary of TCAB and TCAOB Translocation Data in Soybeans . .	14
5-1	Incidence of Resorptions and Malformations in TCAOB-Treated Mice and in Controls	21
5-2	Incidence of Cleft Palate in Transplanted and Nontransplanted DBA and NMRI Mice Treated with TCAOB	24
5-3	Effect of TCAB and TCAOB on the Body Weight and Organ Thymus Weight of Rats	28
9-1	Composite Scores for the Toxicity of TCAB and TCAOB.	42
9-2	TCAB Minimum Effective Dose (MED) and Reportable Quantity (RQ).	43
9-3	TCAOB Minimum Effective Dose (MED) and Reportable Quantity (RQ).	44
9-4	TCHB Minimum Effective Dose (MED) and Reportable Quantity (RQ).	45

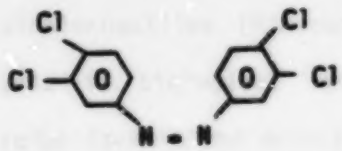
LIST OF ABREVIATIONS

ADI	Acceptable daily intake
Ah	Aryl hydrocarbon
BUN	Blood urea nitrogen
bw	Body weight
CAS	Chemical Abstracts Service
CS	Composite score
DNA	Deoxyribonucleic acid
ED_{50}	Median effective dose
GC	Gas chromatography
HDL	High density lipoprotein
HPLC	High performance liquid chromatography
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
MS	Mass spectrometry
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TCAB	Tetrachloroazobenzene
TCAOB	Tetrachloroazoxybenzene
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCHB	Tetrachlorohydrazobenzene

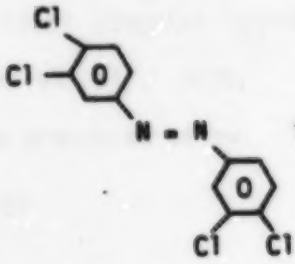
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

3,3',4,4'-TCAB, also called bis(3,4-dichlorophenyl) diazene, is a contaminant in commercial 3, 4-dichloroaniline and in the herbicides synthesized from it (e.g., propanil, linuron, diuron, neburon) (Sundstrom et al., 1978; Bunce et al., 1979; Hill et al., 1981). In addition, it is formed in the environment by the photolysis and biolysis of 3,4-dichloroaniline (Mansour et al., 1975; Kaufman et al., 1972) (Chapter 2). Its structure, molecular formula and molecular weight are given below:



cis-isomer



trans-isomer

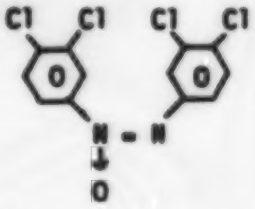
Molecular formula: $C_{12}H_6Cl_4N_2$

Molecular weight : 320.0

The CAS Registry number for TCAB is 14047-09-7.

TCAOB, also called bis(3,4-dichlorophenyl) diazene-1-oxide, is a yellowish orange crystalline solid (Hsia and Burant, 1979) present as a contaminant in at least one anilide herbicide (diuron) (Sundstrom et al., 1978) and is formed in the environment by the photolysis and biolysis of 3, 4-dichloroaniline (Mansour et al., 1975; Kaufman et al., 1972) (Chapter 2).

Its structure, molecular formula and molecular weight are given below:

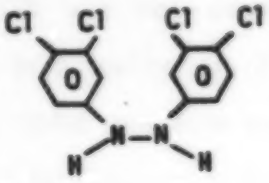


Molecular formula: $C_{12}H_6Cl_4N_2O$

Molecular weight : 336.0

The CAS Registry number for TCAOB is 21232-47-3.

TCHB, also called 1,2-bis(3,4-dichlorophenyl) hydrazine, is a pale yellow crystalline solid (Hsia and Burant, 1979) formed by the photolysis of 3,4-dichloroaniline (Mansour and Korte, 1976) (Chapter 2), and possibly by biolysis in biological systems (Kaufman et al., 1972). Its structure, molecular formula and molecular weight are presented below:



Molecular formula: $C_{12}H_8Cl_4N_2$

Molecular weight: 322.0

The CAS Registry number for TCHB is 71753-42-9.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

TCAB:

Melting point (°C):	158 (Corbett and Holt, 1963)
Log Octanol/Water partition coefficient (calculated):	6.69 (GEMS, 1984)
Solubility in water (calculated):	1 µg/l (Lyman et al., 1982)
Log K_{oc}	6.48 (calculated using regression equation 4.10 on p. 4-9 of Lyman et al., 1982)

TCAOB:

Melting Point (°C):	139 (Gandry and Keirstead, 1949a)
Log K_{oc}	Not possible to estimate from the available data

TCHB:

Melting Point (°C):	136-137 (Gandry and Kirstead, 1949b)
Log Octanol/water partition coefficient (calculated):	5.81 (GEMS, 1984)
Solubility in water (calculated):	20 µg/L (Lyman et al., 1982)
Log K_{oc}	5.6 (calculated using regression equation 4-10 on p. 4-9 of Lyman et al., 1982)

1.3. PRODUCTION DATA

TCAB, TCAOB and TCHB are not commerically manufactured. They are unwanted contaminants, principally of 3,4-DCA and its derivatives. In addition to this, TCAB, TCAOB and TCHB are also produced by microbial, and possibly by photochemical degradation of 3,4-DCA and its derivate.

There are three reports concerning the occurrence of TCAB and TCAOB quantification in 3,4-dichloroaniline and in some herbicides derived from DCA (Table 1-1) (Bunce et al., 1979; Sundstrom et al., 1978; Hill et al., 1981). These sources reported a range of 9-8550 µg TCAB/g 3,4-dichloroaniline; Hill et al. (1981) reported one instance of TCAOB in 3,4-dichloroaniline (8 µg/g). Because this range spans almost 3 orders of magnitude for TCAB, a range, rather than an average of production values was calculated since it is not known what values of TCAB contamination are the most representative.

TABLE 1-1

TCAB and TCAOB Contamination Levels in Anilide Herbicides and 3,4-Dichloroaniline

Compound	Year of Sampling	Concentration (µg/g) TCAB	Concentration (µg/g) TCAOB	Reference
3,4-Dichloroaniline	NA	51	8	Hill et al., 1981
3,4-Dichloroaniline	NA	9	NA	Hill et al., 1981
3,4-Dichloroaniline	NA	22	NA	Hill et al., 1981
3,4-Dichloroaniline	NA	8550	NA	Bunce et al., 1979[a]
3,4-Dichloroaniline	NA	90	NA	Bunce et al., 1979[a]
3,4-Dichloroaniline	NA	60	NA	Bunce et al., 1979[a]
3,4-Dichloroaniline	1973	180	<0.1	Sundstrom et al., 1978
3,4-Dichloroaniline	1978	460	<0.1	Sundstrom et al., 1978
3,4-Dichloroaniline	1978	13	<0.1	Sundstrom et al., 1978
Propanil	NA	1400	NA	Hill et al., 1981
Propanil	NA	1000	NA	Hill et al., 1981
Propanil	NA[b]	2700	NA	Bunce et al., 1979[a]
Propanil	NA[c]	2350	NA	Bunce et al., 1979[a]
Propanil	NA[c]	2150	NA	Bunce et al., 1979[a]
Propanil	NA[c]	2350	NA	Bunce et al., 1979[a]
Diuron	NA	28	NA	Hill et al., 1981
Diuron	NA	28	NA	Hill et al., 1981
Diuron	1976[d]	16	<0.05	Sundstrom et al., 1978
Diuron	1975[e]	7.3	0.30	Sundstrom et al., 1978
Diuron	1976[e]	28	0.75	Sundstrom et al., 1978
Diuron	1978[e]	8.7	1.9	Sundstrom et al., 1978
Diuron	1978[e]	5.6	1.1	Sundstrom et al., 1978
Linuron	NA	9	NA	Hill et al., 1981
Linuron	1978[f]	8.8	<0.05	Sundstrom et al., 1978
Linuron	1978[f]	9.4	<0.05	Sundstrom et al., 1978
Linuron	1978[f]	7.5	<0.05	Sundstrom et al., 1978
Neburon	NA	ND	NA	Hill et al., 1981
Methazole	NA	detected	NA	Welch, 1981

[a]Average of two analyses
[b]Granular, technical
[c]Emulsifiable liquid
[d]Technical
[e]Formulation, 800 g/kg
[f]Formulation, 500 g/kg
NA = Not available; ND = not detectable

The initial TSCA inventory gives a production volume for 3,4-dichloroaniline of 100,000-1,000,000 lbs/year, which yields a TCAB production rate of 0.41-3900 kg/year and a TCAOB production rate of 0.36-3.6 kg/year.

The above calculation probably provides the limits of TCAB production during manufacturing processes, assuming that no TCAB is produced subsequently during the use of 3,4-dichloroaniline (i.e., in the manufacture of propanil). No information was found in the available literature to confirm this assumption. Since 3,4-dichloroaniline is used as a precursor to dyes, and is used to a limited extent as a heat transfer fluid in addition to its use in the manufacture of herbicides (Kao and Poffenberger, 1979), TCAB may find its way into a number of products. The amount of TCAB and related compounds in 3,4-dichloroaniline may be reduced by the use of a bisulfite/metabisulfite reducing couple during the hydrogenation of 3,4-dichloronitrobenzene; no data on its effectiveness were available (Kulkarni and Conway, 1979).

1.4. USE DATA

Pertinent data regarding uses for TCAB, TCAOB, or TCHB were not located in the available literature cited in the Appendix.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

TCAB, TCAOB and TCHB are formed in the environment from the dimerization of 3,4-dichloroaniline by either a chemical or biochemical pathway. 3,4-Dichloroaniline, in turn, enters the environment principally from the hydrolysis of anilide herbicides including propanil, linuron, diuron, and neburon. The majority of the available literature is devoted to a description of how TCAB, TCAOB and TCHB are formed in the environment, rather than a discussion of their environmental fate.

2.1. AIR

Pertinent data regarding the formation or degradation of TCAB, TCAOB or TCHB in air were not located in the available literature cited in the Appendix. Mansour et al. (1975) irradiated 3,4-dichloroaniline in water, methanol, and a 1:1 mixture of water and ethanol with light <290 nm and found no TCAB, TCAOB, or TCHB present in the product mixture.

2.2. WATER

TCAB, TCAOB, and TCHB appear to be formed in water from the photolysis of 3,4-dichloroaniline, while the biodegradation of 3,4-dichloroaniline results in the formation of only TCAB and TCAOB. No studies were found that described the photolysis or biological breakdown of the title compounds.

Mansour et al. (1975) and Mansour and Korte (1976) described the direct photolysis of 3,4-dichloroaniline in water and water/methanol (1:1) using a medium pressure mercury lamp and wavelengths >290 nm. In water, TCAB and TCAOB were formed from 3,4-dichloroaniline in yields of 7 and 4%, respectively, after 25 hours of irradiation (Mansour et al., 1975). Evidence was found for the formation of TCAOB first, followed by its decomposition to

TCAB. Mansour and Korte (1976) reported that both TCAOB and TCHB are formed in methanol water (1:1) from the photodimerization of 3,4-dichloroaniline and that both compounds lead to TCAB formation.

Moilaneu and Crosby (1972) reported that propanil, when photolyzed in distilled water by either sunlight or simulated sunlight, decomposes initially to 3,4-dichloroaniline; photodimerization of 3,4-dichloroaniline then produces TCAB. The photolysis of propanil is relatively slow and produces a very complex GC profile that changed with time. 3,4-Dichloroaniline decomposes rapidly to form (presumably among other compounds) TCAB.

In contrast, Miller et al. (1980) reported that no TCAB was formed when 3,4-dichloroaniline in distilled water was photolyzed with sunlight. TCAB was formed when either humic acid was added to the water or when natural rice field waters were used. The authors suggested that this and other evidence presented indicates that direct photolysis does not lead to the formation of TCAB while the use of photosensitizers does. The mechanism presented to describe the photolytic reactionsinvolved hydrogen abstraction by compounds present in water, followed by a dimerization to TCHB and oxidation to TCAB. TCAOB was not reported to be present.

Miller et al. (1980) also reported that previous work has shown that 2-chloro-5-aminophenol is the major (>78%) direct photolysis product of 3,4-dichloroaniline in distilled water, with minor amounts of the dechlorination product 3-chloroaniline also present. Neither Mansour et al. (1975) nor Mansour and Korte (1976) report any phenols being present in the product mixture from the direct photolysis of 3,4-dichloroaniline. Insufficient detail was given in the experimental section of these two studies to determine whether phenolic products could have eluded the analytical methods used. Although this cannot be resolved with the information available, it is possible that 2-chloro-5-aminophenol was overlooked.

The formation of TCAB in aqueous systems from the microbial transformation of propanil has been studied mainly in rice paddy waters and soils. Deuel et al. (1977) sprayed 99% pure propanil on rice cultivars (Beaumont clay) at 3.4 and 6.4/kg/ha (~60 µg/g in soil recovered at time of application), 24 hours before flooding with 10 cm of water. Propanil residues in the water dissipated almost completely within 24 hours after flooding the cultivars with either impounded or flowing water. 3,4-Dichloroaniline concentrations in the water increased with decreasing propanil concentrations. Concentrations of 3,4-dichloroaniline in water decreased from 24-336 hours with a concomitant rise in the soil concentration. At no time was TCAB found in either the water or the soil (detection limits were 0.2 µg/L in water and 0.004 µg/g in soil).

Isensee et al. (1982) treated microecosystems designed to simulate a rice paddy with ring-labeled ^{14}C-3,4-dichloroaniline (equivalent to 1.3 kg DCA/ha). Matapeake loam (pH = 5.3; organic matter content = 1.5%) was treated with 3,4-dichloroaniline then moistened to field capacity and watered as needed for 15 days. After 15 days, the soil was flooded with 3 cm of water. TCAB was never detected in the water, but depending upon the exposure time, between 6 and 19% of the extractable radioactivity in the soil was attributable to TCAB. The major difference between these two studies appears to be that the study of Deuel et al. (1977) established anaerobic conditions within 24 hours of propanil application; whereas, 15 days of aerobic incubation was allowed in the study by Isensee et al. (1982). The need for aerobic conditions for the formation of TCAB appears to agree with data presented in the study by Sprott and Corke (1971) in the following section.

2.3. SOIL

TCAB and TCAOB are formed in soil from the dimerization of 3,4-dichloroaniline, which has been related to the peroxidase activity of the soil, although alternative mechanisms (i.e., diazotization followed by coupling) may also be important. TCAB and TCAOB sorb very strongly to soils and are not likely to leach.

Many studies describe the formation of TCAB both in soil (Bordeleau and Bartha, 1970, 1972a,b; Bartha et al., 1968; Bartha and Pramer, 1970; Kaufman et al., 1971; Sprott and Corke, 1971; Burge 1972, 1973; Kearney and Plimmer, 1972; Buser and Bosshardt, 1975; Sotiriou et al., 1976; Hughes and Corke, 1973; Lee and Fournier, 1978) and by soil microorganisms (Bartha, 1971; Bollag, 1972; Kaufman et al., 1972; Bordeleau and Bartha, 1971, 1972c; Lee and Kim, 1978; Lay and Ilnicki, 1974; Bunce et al., 1983). The majority of these studies relate TCAB production to peroxidase activity in the soil (Bordeleau and Bartha, 1970, 1971, 1972a,b,c; Lay and Ilnicki, 1974; Bartha et al., 1968; Bartha, 1971; Burge, 1973); however, other mechanisms, such as diazotization, have been suggested (Corke et al., 1979; Bunce et al., 1979).

Most workers have suggested that the initial step in TCAB formation from anilide herbicides is the hydrolysis of the anilide to yield 3,4-dichloroaniline, although labile intermediates such as phenylhydroxylamines and nitrosobenzenes have been suggested by others (Bourdeleau and Bartha, 1970; Kaufman et al., 1972). Both phenylhydroxylamines and nitrosobenzenes lead to the formation of TCAOB followed by decomposition to TCAB. Corke et al. (1979) trapped what they suggested was a diazonium ion with 2-naphthol from a growth medium containing Escherichia coli, indicating that the diazonium ion was an intermediate in the formation of TCAB.

Sprott and Corke (1971) found that TCAB is formed from 3,4-dichloroaniline more readily under aerobic conditions than anaerobic conditions. Under anaerobic conditions, sterile and nonsterile soils produced the same amount of TCAB, indicating that the formation process under these conditions is chemical and not biochemical. Hughes and Corke (1973) found soil pH was a factor in determining TCAB yield from either propanil or 3,4-dichloroaniline, and Bartha (1971) reported that soil samples that had been dried in the laboratory before treating with 3, 4-dichloroaniline showed reduced TCAB producing activity.

TCAB, TCAOB, and TCHB disappearance in the environment has not been well studied. Kearney et al. (1970) reported residual levels of both propanil (0.01-0.3 ppm, depending on depth of soil examined) and TCAB (0.01 ppm) in field (rice producing) soils treated once with 4.5-10.0 kg/ha propanil 2 years before the sampling. The occurrence of TCAB in the soil was reported to be related to rate of application and time elapsed since propanil application.

Kearney et al. (1970) also applied propanil to a different plot of these soils at 3.4 and 6.7 kg/ha and then measured TCAB concentrations. TCAB was found in 2 of 4 sampling areas when propanil was applied at 3.4 kg/ha, but all sampling areas were positive when the application rate was 6.7 kg/ha. The maximum concentration measured was 0.18 ppm with an average concentration of 0.09 ppm (at the 6.7 kg/ha rate). Although the TCAB formation in this study is much lower than in some laboratory studies, residue rates are substantially higher than those reported by Deuel et al. (1977).

Kearney et al. (1970) reported that the majority of the TCAB present in a field study was found in the upper 0-10.1 cm horizon of the soil. A field treated with 13.5 kg propanil/ha, ~14 days before sampling had 0.16 ppm TCAB

in the 0-10.1 cm horizon, 0.03 ppm in the 10.1-20.2 cm horizon and 0.02 ppm in the 20.2-30.5 cm horizon. Soils treated with 9 kg propanil/ha, 1 year before sampling had TCAB residues of 0.01-0.02 ppm in the 0-10.1 cm horizon, and 0.01-0.05 ppm in the 10.1-20.2 cm horizon. No TCAB was detected (0.01 ppm detection limit) below 20.2 cm. Soils that received 4.5-10.0 kg propanil/ha 2 years before sampling had TCAB residues at the detection limit (0.01 ppm) in the 0-10.1 cm horizon only.

Kearney et al. (1970) reported that propanil has a short residual life in most soils. Application rates of 6.7 kg/ha generally resulted in residues <0.01 ppm in Arkansas soil just 40 days later. Absence of a quantitative transformation to TCAB was indicated to strongly suggest the occurrence of competitive reactions within the soil, and it was further suggested that DCA may be lost to volatility or absorption by rice plants. Also, since propanil must undergo a number of intermediate steps in the formation of TCAB, localized conditions in any soil plot may favor one route over another. No definitive half-life values were determined for either propanil or TCAB.

3. EXPOSURE

Only two monitoring reports are available for TCAB. Kearney et al. (1970) found TCAB in 2 of 4 sampling sites (0.02 and 0.05 ppm, detection limit = 0.01 ppm) in a 0.21 ha rice plot treated with 3.4 kg propanil/ha. When the application rate was increased to 6.7 kg propanil/ha, TCAB was found in all four sampling sites with an average of 0.09 ppm. Propanil was found in two of the sites receiving 3.4 kg/ha and one site receiving 6.7 kg/ha. Kearney et al. (1970) also found 0.16 ppm TCAB present in the 0-10.1 cm level of a rice field plot that had received two propanil applications, one 4.5 kg propanil/ha application 2 years before sampling and one 13.5 kg/ha ~14 days before the sampling. TCAB was also found in the 10.1-20.2 cm level (0.03 ppm) and in the 20.2-30.5 cm level (0.02 ppm).

Kearney et al. (1970) also found that soils that received propanil applications of 9 kg/ha had TCAB residues 1 year after treatment. TCAB residues were found at all four sampling sites in the 1-10.1 cm level (0.01-0.02 ppm) and in 2 of the 4 sites at the 10.1-20.2 cm level (0.01 and 0.05 ppm). No TCAB was found in the 20.2-30.5 cm range. TCAB residues at the detection limit (0.01 ppm) were also found in soils that received 4.5-10.0 kg propanil/ha 2 years before sampling. These residues were only present in the 0-10.1 cm horizon.

Kearney et al. (1970) also reported that TCAB residues (average 0.03 ppm) were found in soils that received no propanil applications. The authors suggested that these residues may have been the result of cross contamination during sampling and analysis, spray drift of propanil from treated to untreated plots, and irrigation water transfer of TCAB and propanil (or both).

Carey et al. (1980) sampled 99 sites in 1972 during late summer in Arkansas, California, Louisiana, Mississippi, and Texas. Each site represented about 6073 ha, and the number of sites sampled in each state was proportional to the amount of land used for rice production in those areas. TCAB was found in 6 of the 99 sites at levels ranging from 0.01-0.05 ppm dry weight.

Although monitoring data were not located in the available literature, TCAB residues potentially could be found in plant residues from treated soils. Still (1969) found that TCAB, added to a nutrient (Hoagland's) solution, is translocated to growing rice plants. Of the TCAB present, 5.6% was taken up by the entire plant while 3.2% was translocated to the shoots. TCAB was not present in the plants when the nutrient solution contained propanil or 3,4-dichloroaniline. Isensee et al. (1982) observed that only 0.31-0.49% of the radioactivity (applied as ^{14}C-3,4-dichloroaniline) was present in rice plants in a model ecosystem.

Worobey (1984) sprouted soybean plants for 9 days in a commercial-type sprouter, and then planted them in three soils containing 0, 1.7, and 57% organic matter. The soils had previously been treated with TCAB incorporated at a level of 25 ppm. The plants were harvested 12 days after planting. TCAB and TCAOB were detected in the soil and roots while only TCAB was detected in the shoots. More TCAB and TCAOB were translocated in roots and shoots from the pure sandy soil (0% organic matter) than from other soils. These data are summarized in Table 3-1.

Viswanathan et al. (1978) treated outdoor plots with 1.43 kg ^{14}C-3,4-dichloroaniline/ha, then planted barley immediately afterward. After the first year, 69.8% of the applied radioactivity was present in the recovered soil, plants and leached water. An unidentified amount of TCAB was found in

TABLE 3-1

Summary of TCAB and TCAOB Translocation Data in Soybeans[a]

Soil Organic Matter (%)	Concentration (ppm)					
	Soil[b]		Roots[c]		Shoots[d]	
	TCAB	TCAOB	TCAB	TCAOB	TCAB	TCAOB
0	8.72	0.043	57.5	0.317	0.620	ND
1.7	7.94	0.021	58.4	0.289	0.492	ND
57	5.90	0.020	14.4	ND	0.178	ND

[a]Source: Worobey, 1984

[b]80% field capacity

[c]88.7% moisture

[d]82.8% moisture

ND = Not detected, detection limit 0.01 ppm

the soil and barley. The presence of TCAB in the barley grains could not be determined unequivocally; however, if present it was "well below" 0.005 µg/g.

4. PHARMACOKINETICS

Limited pertinent data regarding the absorption, distribution, metabolism or excretion of TCHB were located in the available literature cited in the Appendix.

4.1. ABSORPTION

The urinary excretion data from the gavage experiments of Burant and Hsia (1984) (Section 4.4.) imply that at least ~27% of the administered dose of TCAB and at least ~20% of the administered dose of TCAOB were absorbed from the gastrointestinal tract of rats. The mortality data in rats from short-term inhalation studies and systemic toxicity to rabbits in skin application studies of Sundstrom (1980) imply that TCAB is absorbed, at least in part, after inhalation or dermal exposure (Section 5.6.). Additional pertinent data regarding the absorption of TCAB or TCAOB were not located in the available literature cited in the Appendix.

4.2. DISTRIBUTION

The distribution of radioactivity was studied by Burant and Hsia (1984) in two male Sprague-Dawley rats 5 days after they had been treated by gavage with 10 mg of ^{14}C-TCAB or ^{14}C-TCAOB (position of label not specified). Radioactivity following either treatment was distributed widely, with tissue levels ranging from 0.0012-0.0497% dose/g wet tissue. The highest concentration of radioactivity from ^{14}C-TCAB or ^{14}C-TCAOB was found in the epididymal fat, while the lowest concentration of radioactivity for ^{14}C-TCAB or ^{14}C-TCAOB was found in the brain.

4.3. METABOLISM

Hsia and Kreamer (1981) incubated ^{14}C-labeled TCAB (position of label not specified) <u>in vitro</u> with an NADPH-generating system and microsomes from

male Sprague-Dawley rats, which had been injected intraperitoneally with 25 mg/kg/day of TCAOB in corn oil (5 mg/mL) for 5 consecutive days. Control microsomes were obtained from rats that had received 5 mL/kg/day plain corn oil. HPLC and GC-MS identified TCAB phenol (exact structure unspecified) as the most abundant metabolite *in vitro*. TCHB, dichlorophenol and azodichlorophenol were also identified. Significant covalent binding of radioactivity to cellular macromolecules in conjunction with the identification of TCAB phenol as a metabolite of TCAB suggested to Hsia and Kreamer (1981) that a reactive epoxide intermediate, most likely the 5,6-arene oxide of TCAB, may be generated during the *in vitro* metabolism of TCAB.

4.4. EXCRETION

Groups of four male Sprague-Dawley rats were given 10 mg of ^{14}C-TCAB or ^{14}C-TCAOB in corn oil by gavage (Burant and Hsia, 1984). The urine and feces were collected at 24-hour intervals for 5 consecutive days. The recovery of 66 or 37% of the administered radioactivity from rat urine and feces within 24 hours of ^{14}C-TCAB or ^{14}C-TCAOB treatment, respectively, indicated that TCAB is eliminated more rapidly than TCAOB. Within 48 hours of ^{14}C-TCAB treatment, a total of 82% of the administered radioactivity was recovered, 27.1$\pm$3.8% from the urine and 55.1$\pm$4.9% from the feces. Within 48 hours of ^{14}C-TCAOB treatment, only 70% of the administered radioactivity was recovered, 20.1$\pm$1.8% from the urine and 50.0$\pm$14.3% from the feces. Little radioactivity was recovered from urine and feces collected between 2 and 5 days after dosing with ^{14}C-TCAB or ^{14}C-TCAOB indicating that excretion was essentially complete in 2 days.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of TCAOB and TCHAB were not located in the available literature cited in the Appendix.

The carcinogenic potential of TCAB is demonstrated by its ability to induce the morphological transformation of mouse embryo fibroblasts *in vitro* (Hsia, 1981). This experiment is described in more detail in Section 5.2.

In a study reviewed by Bartha and Pramer (1970), rats were fed 4 mg/week of TCAB in peanut oil for the first 3 weeks and 10 mg/week for the next 37 weeks. The animals were then observed until 60 weeks after the initiation of treatment. No tumors were observed in treated rats, although fatty degeneration in the liver was reported after 60 weeks. Additional details of this study were not provided.

5.2. MUTAGENICITY

Neither TCAB nor TCAOB, in concentrations ranging from 1-2000 µg/plate, induces reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1530, TA1535, TA1537, TA1538, TA1532, TA1950, TA1975, TA1978 and G46 when studied by plate incorporation with or without metabolic activation under aerobic or anaerobic conditions (Gilbert et al., 1980). In the fluctuation test, however, TCAB shows a statistically significant ($p<0.05$) but marginal mutagenic activity: <2-fold greater response than control was reported in the TA1538 and TA1532 strains of *S. typhimurium* in the presence of the S-9 fraction after incubation with TCAB at 1.25 and 2.5 mg/mL. The significance of their increase in mutagenic activity was debatable (Gilbert et al., 1980).

Hsia et al. (1977) reported ~0.5 revertants/μg of TCAB (0.20 revertants/nmol) above the spontaneous rate in S. typhimurium strain TA98. The response was reported to be dose-related at concentrations >100 μg of TCAB/plate. Additional details of this assay were not provided.

In another study, incubation of Aspergillus nidulans spores with 5-200 μg/mL of TCAB for 5 days resulted in an increased frequency of back mutations, but the increase did not appear to be dose-related (Prasad, 1970).

Hepatocytes freshly isolated from 2-month-old Sprague-Dawley rats were incubated for 1 hour with TCAB (10^{-6} to $5x10^{-4}$ M), washed in ice-cold incubation medium, and suspended again in the incubation medium containing ^{3}H-thymidine and cultivated for 3 hours (Hsia and Kreamer, 1979a). TCAB caused a dose-related increase in the amount of unscheduled DNA synthesis at concentrations up to $5x10^{-5}$ M.

Mouse embryo fibroblasts, C3H/10T1/2, incubated with 1 μg/mL of TCAB for 10 days no longer display contact inhibition and develop focal morphological alterations, consisting of thickened spindle shaped cells arranged in swirls, called type III foci (Hsia et al., 1977; Hsia, 1981). Type III foci are reported to be characteristic of transformed cells (Hsia et al., 1977). Transplantation of cells from type III foci into syngeneic C3H mice resulted in the formation of tumors (Reznikoff et al., 1973).

Pertinent data regarding the mutagenicity of TCHB were not located in the available literature cited in the Appendix.

5.3. TERATOGENICITY

The teratogenic sensitivity to TCDD and its congeners TCDF and TCAOB is strain-dependent in the mouse. Groups of 10-11 pregnant C57BL mice were given a single intraperitoneal injection of 6 mg/kg bw of TCAOB on day 10, 11, 12 or 13 of gestation (Hassoun et al., 1984). Groups of 5-7 pregnant

C57BL mice treated intraperitoneally with 320 µL/kg bw dioxane, the solvent for TCAOB, on days 10, 11, 12 or 13 of gestation were considered the control group. One group of nine pregnant C57BL mice received intraperitoneal injections of 16 mg/kg bw of TCAOB on day 12 of gestation. The morning after mating on which a vaginal plug was present was considered day 0 of gestation.

In the same study, groups of 7-9 pregnant DBA mice and groups of 7-8 pregnant AKR mice were given a single intraperitoneal injection of 8 mg/kg bw of TCAOB on day 10, 11 or 12 of gestation. One group of nine DBA mice received an intraperitoneal injection of 16 mg/kg of TCAOB on day 12 of gestation. No control groups were reported in the DBA and AKR mouse strains. The results, summarized in Table 5-1, indicate that 6 mg/kg TCAOB injected intraperitoneally caused increased incidences of resorption, cleft palate, hydronephrosis and hydrops in the offspring of C57BL mice. No signs of maternal toxicity were reported. The incidence of both cleft palate and hydronephrosis was highest when the mice were treated on day 11 of gestation. The incidence of resorptions appeared to decrease, but the incidence of hydrops appeared to increase, as the day of treatment occurred later in gestation. Increasing the dose of TCAOB to 16 mg/kg bw on day 12 of gestation increased the resorption rate to 60% and resulted in cleft palate in 95% of the remaining fetuses. As indicated in Table 5-1, treatment of strains DBA and AKR mice on day 10, 11 or 12 of gestation with 8 mg/kg TCAOB did not result in an incidence of resorptions, cleft palate, hydronephrosis or hydrops substantially higher than the incidence reported for the dioxane-treated control C57BL mice. Lack of DBA and AKR controls, however, limits the interpretation of the data presented on TCAOB-treated DBA and AKR mice.

TABLE 5-1

Incidence of Resorptions and Malformations in TCAOB-Treated Mice and in Controls[a]

Strain	Treatment (mg/kg)	Day of Gestation Treated	Number of Implantations	Percent Resorptions[b]	Percent with Cleft Palate[c]	Percent with Hydronephrosis	Percent with Hydrops
C57BL	vehicle control	10	46	19.6	0	0	0
		11	52	15.4	4.5	0	0
		12	35	14.3	0	12.5	0
		13	33	18.2	0	0	0
C57BL	6	10	77	31.2	33.6	63.0	0
		11	77	28.6	64.7	79.3	5.1
		12	80	21.3	56.6	37.3	8.1
		13	82	19.5	23.0	26.9	7.9
	16	12	50	60.0	95.0	NI	2.0
DBA	8	10	54	5.6	1.9	2.0	0
		11	50	20.0	5.0	0	0
		12	48	8.3	2.3	0	0
	16	12	52	38.4	3.1	NI	0
AKR	8	10	38	10.5	0	2.9	0
		11	34	14.7	0	10.3	0
		12	40	7.5	2.7	2.7	0

[a]Source: Hassoun et al., 1984

[b]Resorptions were identified either as "early deaths," which were fetuses <6 mm in length, or "late deaths," which were fetuses >6 mm in length.

[c]The percentage of fetuses with cleft palate was based on the number of late stage fetuses that were possible to investigate. The number of fetuses with cleft palate was not reported.

NI = Not investigated

When DBA mice received 8 mg/kg of TCAOB on day 12 of gestation, 8.3% of the implantations were resorbed. Treatment of DBA mice with 16 mg/kg of TCAOB on day 12 of gestation increased the incidence of resorptions to 38.4%, but had no apparent effect on the incidence of cleft palate.

TCAOB treatment (6-8 mg/kg on day 12 of gestation) of groups of mice from inbred strains (C57BL, AKR, NMRI and DBA) and some crosses and backcrosses between these strains indicated that nonsensitivity to the development of cleft palate segregates as a dominant trait in the crosses of C57BL and NMRI mice. In crosses between NMRI and DBA mice, however, the data suggested that the maternal strain may modulate the susceptibility of the offspring to cleft palate development (Hassoun et al., 1984).

In another study, 10 pregnant sensitive (NMRI) mice and 11 pregnant resistant (DBA) mice received an intraperitoneal injection of 8 mg/kg bw of TCAOB on day 12 of gestation (D'Argy et al., 1984). Day 0 of gestation was defined as the day on which vaginal plugs were present. The pregnant dams were killed on day 16 or 17 of gestation, and the fetuses were examined. On day 2 of pregnancy (10 days before treatment) each NMRI mouse had received by a micropipette inserted into the cervical end of the uterus 4-6 blastocysts, which had been flushed from the uterus of a DBA dam killed on day 3 of pregnancy. In a similar manner, also on day 2 of pregnancy, each DBA mouse received 4-6 blastocysts, which had been flushed from the uterus of an NMRI mouse killed on day 3 of pregnancy. Therefore, each mouse carried embryos of its own strain as well as embryos of the other strain. The blastocysts were transplanted in order to evaluate the relative importance of the maternal environmental effect as opposed to genetic expression. The TCDD-sensitive NMRI mice carry the Ah-receptors found in high concentrations in the cytoplasm of pharyngeal cells during midgestation; the TCDD-resistant

DBA mice do not. The Ah-receptor protein is coded at the Ah-locus and is known to bind strongly with polynuclear aromatic compounds such as TCDD (Poland and Knutson, 1982). Because TCAOB and TCDD are isosteric and because TCDD is known to cause cleft palate, D'Argy et al. (1984) tested the hypothesis that binding of TCAOB to the Ah-receptor protein is a causative in the development of birth defects. As indicated in Table 5-2, almost all the NMRI fetuses displayed cleft palate when examined on day 16 or 17 of gestation regardless of the maternal environment. Cleft palate was not observed in any of the DBA fetuses when examined on day 16 or 17 of gestation, regardless of the maternal environment.

TCAB and TCAOB are embryotoxic and teratogenic when injected into the air cell of fertilized and developing chicken eggs, causing primarily rump edema (Schrankel et al., 1982). Other abnormalities included altered feather pattern, lack of down, hemorrhage, external viscera, reduced body size, beak malformation and micropthalmia. Although TCAOB was more toxic than TCAB, both were more toxic to the chick embryo than any other chemical tested in the chick embryo system except TCDD (Schrankel et al., 1982).

Using the data on C57BL mice from Hassoun and Dencker (1982) and Hassoun et al. (1984), a comparison of the teratogenic effectiveness of TCDD, TCDF and TCAOB can be made. Based upon ED_{50} values, the relative potencies of these three compounds would be 1, 0.125 and 0.005 for TCDD, TCDF and TCAOB, respectively.

Pertinent data regarding the teratogenicity of TCHB and TCAB, with the exception of the chick embryo data reported above, were not located in the available literature cited in the Appendix.

TABLE 5-2

Incidence of Cleft Palate in Transplanted and Non-transplanted DBA and NMRI Mice Treated with TCAOB*

Donors	Recipients	Number of Implantations	DBA		NMRI		Number of Dead Plus Resorbed Fetuses
			Live Fetuses	Number with Cleft Palate	Live Fetuses	Number with Cleft Palate	
DBA	NMRI	9	1	0	7	7	1
		13	1	0	12	9	0
		2	2	0	0	0	0
		11	1	0	6	5	4
		10	1	0	7	7	2
		10	3	0	5	4	2
		10	1	0	8	8	1
		13	2	0	9	9	2
		2	2	0	0	0	0
		10	1	0	8	7	1
NMRI	DBA	8	6	0	1	1	1
		7	5	0	1	1	1
		6	4	0	2	1	0
		3	1	0	1	1	1
		4	0	0	2	2	2
		6	3	0	1	1	2
		4	1	0	2	2	1
		3	2	0	1	1	0
		3	2	0	1	1	0
		6	4	0	1	1	1
		2	0	0	1	1	1

*Source: D'Argy et al., 1984

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of TCAB, TCAOB or TCHB were not located in the available literature cited in the Appendix.

5.5. CHRONIC TOXICITY

No long-term studies of TCAB, TCAOB or TCHB exposure of animals were located in the available literature; however, a subchronic feeding study (Hsia et al., 1980) and several short-term studies using the intraperitoneal route of administration (Hsia et al., 1981, 1982; Hinsdill et al., 1984; Olson et al., 1984; Schrankel et al., 1980) describe toxic effects of TCAB and TCAOB in rodents. In addition, the toxic effects of dermally applied TCAB or TCAOB in rabbits have been studied (Hill et al., 1981; Taylor et al., 1977), and there are several reports of human occupational exposure studies were available (Taylor et al., 1977; Taylor and Lloyd, 1982; Scarisbrick and Martin, 1981; Taylor, 1979; Morse and Baker, 1977).

In the subchronic study, groups of 10 male Sprague-Dawley rats weighing 150 g were exposed to 100 ppm of TCAB in the diet, 100 ppm of TCAOB in the diet, or control diets for 120 days (Hsia et al., 1980). Records of food consumption and body weight were kept, but not reported. The total amounts of TCAB and TCAOB actually consumed by each rat during the 120-day period were reported to be 25.2±2.4 mg and 24.0±2.3 mg, respectively. After a 24-hour fast, the rats were killed and blood samples were taken. Hematocrit and hemoglobin determinations as well as red and white blood cell counts were performed. In addition, BUN, cholesterol, total lipids, total bilirubin, SGOT and SGPT levels were determined. Organ weights of liver, spleen, kidney, heart, lung and testes were recorded. Aryl hydrocarbon hydroxylase (AHH) activity was assayed in liver microsomal preparations.

The average weight gain of rats whose diet was contaminated with TCAB was 9.4% less than the weight gain of control rats, while the average weight gain of rats whose diet was contaminated with TCAOB was 16.9% less than the weight gain of control rats. Both decreases were statistically significant (student's t-test) and appeared after 10 days of treatment. TCAB did not produce any significant change in the absolute weights of the liver, spleen, kidney, heart, lung or testes. Treatment with TCAOB significantly increased the absolute weight of the liver ($p<0.05$), spleen ($p<0.05$) and testes ($p<0.005$). Both TCAB ($p<0.05$) and TCAOB ($p<0.001$) significantly depressed hematocrit and total hemoglobin values, although only TCAOB significantly decreased red blood cell counts ($p<0.001$). Neither treatment affected the hemoglobin content per red blood cell or the white blood cell count. Both the amount of microsomal Ah-hydroxylase activity and the levels of cytochrome P-448 were increased after exposure to TCAB and to TCAOB ($p<0.0005$). SGOT levels were increased by TCAB ($p<0.05$) and TCAOB ($p<0.025$). The only other effect reported to have occurred was an increased level of serum lipid in the rats exposed to TCAOB (Hsia et al., 1980).

Groups of six male Sprague-Dawley rats were treated with weekly intraperitoneal injections of 25 mg/kg/week of TCAB or TCAOB in corn oil for 60 days (Hsia et al., 1981). A group of six male Sprague-Dawley rats that received 2.5 mL/kg/week of corn oil intraperitoneally served as controls. After 60 days of chemical treatment, each animal had received a total dose of 55.0 ± 1.9 mg of TCAB or 54.9 ± 1.9 mg of TCAOB. Two of the six rats that had been treated with TCAOB died by day 60 of the experiment. The remaining rats from all groups were killed on day 60, complete necropsies were performed, the liver, spleen, adrenals, lymph nodes, thymus, kidneys, lung, heart, testes and epididymal fat pad were weighed, and selected samples were

prepared for histological evaluation. As indicated in Table 5-3, the body weight and relative thymus weight of TCAB- and TCAOB-treated rats decreased. TCAOB produced a more severe effect than TCAB. Relative liver weights were reported to be increased 39% above control for TCAB and 55% for TCAOB. Histological alterations were observed in the liver, thymus, lymph node, spleen and lung. Hepatocyte swelling and cytoplasmic vacuoles were observed in the livers of all animals treated with TCAB and TCAOB. Atrophic changes were described in the cortex of the thymus, the outer cortical areas of the mesenteric lymph nodes and the periarterial lymphatic sheaths of the spleen. The lungs of TCAB- and TCAOB-treated animals contained thickened alveolar walls and foamy macrophages, sometimes associated with granulomas (Hsia et al., 1981).

In other studies (Hsia et al., 1982; Olsen et al., 1984; Hinsdill et al., 1984), effects on the thymus and immune system of rats have been observed after only a few intraperitoneal injections of TCAOB. Intraperitoneal injection of 8-week-old rats with 25 mg/kg/day of TCAB or TCAOB on days 1 and 5 of the experiment resulted in a decreased relative thymic weight to 69 or 49% of control weights, respectively, within 11 days of the initial treatment (Hsia et al., 1982). When the same treatment was performed on weanling rats (~3 weeks of age), TCAOB treatment reduced the thymic weight to 31-38% of the control weight. Adrenalectomy did not prevent the drastic reduction in relative thymic weight that was seen in rats exposed to TCAOB. A later study reported that immune parameters showing significant suppression following four single i.p. injections of TCAOB at 25 mg/kg/injection equally spaced over a 17-day period were thymic weight, splenic plaque-forming cell populations and function, peritoneal

TABLE 5-3

Effect of TCAB and TCAOB
on the Body Weight and Organ Thymus Weight of Rats*

Treatment	Body Weight (g)	Thymus Weight (mg)
Controls	320±7	454±30
TCAB	289±13	237±13
TCAOB	283±8	98±5

*Source: Hsia et al., 1981

macrophage chemiluminescence and bone marrow cellularity. Weanling rats were reported to be more susceptible to the immunosuppressive effects of TCAOB than adult rats (Olson et al., 1984).

As reported in the abstract of a study orally presented, Sprague-Dawley rats received four intraperitoneal injections of 25 mg/kg/day of TCAOB within the first 11 days of the study (Hinsdill et al., 1984). The rats were challenged with sheep red blood cells on days 43 and 90 of the experiment. Four days after each sheep red blood cell challenge, the following parameters were evaluated: macrophage function, numbers of splenic plaque-forming cells, hemolysin titer, white blood cell count, hematocrit, plasma protein, bone marrow cellularity and various organ weights. Some parameters were affected more severely after the first sheep red blood cell challenge. For example, the number of plaque-forming cells/10^6 viable lymphocytes was 18% of controls on day 47, but 27% of controls on day 94 of the experiment. Other parameters appeared to be equally affected despite the difference in recovery periods. The investigators stated that long-term residual toxicity following short-term exposure to TCAOB was demonstrated by these results.

Three short-term experiments investigated the hepatotoxicity of TCAB and TCAOB in rats and mice (Schrankel et al., 1980). In the first experiment, an unspecified number of male Sprague-Dawley rats received intraperitoneal injections of 25 mg/kg/day TCAOB in corn oil on days 1 and 5 of the experiment. The rats were killed on day 10 of the experiment and the livers were weighed and prepared for light and electron microscopy. In the second experiment, an unspecified number of rats received a presumably intraperitoneal injection of 25 mg/kg/day of TCAB in corn oil for 4 days. The rats were killed on day 5 of the experiment, and their livers were prepared for light and electron microscopy. In both experiments, groups of control rats

received intraperitoneal injections of corn oil on the same schedule as treated rats. The mitotic index was determined in the livers of the rats treated with TCAOB and with TCAB, and in the livers of control rats by counting the number of mitotic figures/1000 hepatocytes. In the third experiment, an unspecified number of female outbred Swiss albino mice that had just finished lactating received an intraperitoneal injection of 20 mg/kg/day of TCAB for 5 days. The mice were anesthetized with pentobarbital and killed on day 6 of the experiment. The livers were prepared for light and electron microscopy.

Schrankel et al. (1980) reported liver hypertrophy and a significantly increased hepatic mitotic index in rats and mice treated with TCAB or with TCAOB. Post-treatment electromicroscopic examination revealed proliferation of smooth endoplasmic reticulum in hepatocytes and membranous arrays located in electron lucent (low lipid content) vacuoles generally devoid of cytoplasmic organelles. These membranous arrays were also detected to a lesser extent in the sinusoidal spaces after extrusion from the hepatocytes. THe morphogenesis and structure of the TCAOB-induced membrane arrays were reported to be similar to those produced in the rat liver by octabromobiphenyl (Lee et al., 1974), and the arrays appeared to be from either newly synthesized membrane or a structural reorganization of the endoplasmic reticulum membrane.

Hill et al. (1981) painted 0.1 mL of test solutions of TCAB of 0.001-0.08 mg/mL on the inner surface of the left ear of groups of two adult New Zealand rabbits. Applications were made daily for 5 days. The total amounts applied were 0.5-32 µg. The rabbits were killed after 14-22 days of the initial exposure, and the treated ears were examined microscopically. A treatment-related increased severity of hyperkeratosis was

observed. The authors noted that compounds which produce hyperkeratosis in the skin of the rabbit ear generally cause chloracne in workers occupationally exposed to sufficient amounts of these products.

Taylor et al. (1977) applied acetone solutions of TCAOB in concentrations of 0.1, 0.001 and 0.0001% to the ears of albino rabbits, 5 days/week for 4 weeks. At each concentration, chloracne, as evidenced by comedone formation, was observed. The highest concentration also resulted in erythema, edema and necrosis of the epithelium.

These studies were conducted in rabbits to confirm the acnegenic potential of TCAB and TCAOB, since workers engaged in the manufacture of pesticides for which TCAB and TCAOB are extraneous intermediates have developed chloracne. Within a few months after the production of the herbicide, 2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-3,5-dione, was begun, >90% of 41 workers in a small chemical company were reported to have chloracne as a result of exposure to TCAOB, which is an extraneous intermediate formed during the manufacturing process (Taylor et al., 1977). Only one of the 37 workers whose urine samples were analyzed for porphyrin content had a level of 120 mEq/ℓ; the remaining 36 had levels $\leq$100 mEq/ℓ. Three of the 32 workers whose blood samples were analyzed for SGOT content had levels >40 Karmen units. Although inhalation and ingestion were possible ancillary routes of exposure, the principal route of exposure was thought to be dermal. The potency of small amounts of TCAOB is demonstrated by the fact that the family members of four workers contracted chloracne even though they had never been inside the plant. Presumably, the route of exposure for the family members was dermal, from contact with the worker or contaminated clothes or tools of the worker (Taylor et al., 1977).

In a follow-up study 8 years after initial exposure, questionnaires were sent to 15 workers (Taylor and Lloyd, 1982). Of the five who responded, four were photosensitive, three still had some evidence of chloracne, one had mild facial hirsutism and another had hyperpigmentation.

Scarisbruck and Martin (1981) evaluated clinical chemistry parameters related to liver function and lipid abnormalities in 89 workers who had been exposed to TCAB and to lesser amounts of TCAOB in two chemical plants in Great Britain. Of the exposed cohort, 30 workers had chloracne. The plants had been producing diuron and dichloroaniline for ~1-7 years. An age-matched control group (n=90) was drawn from an engineering factory in which there was no exposure to organic chemicals or plastics. The controls were further matched with the exposed workers with respect to height, weight, alcohol intake, smoking habits and drug intake. No significant differences in thymol turbidity or in levels of bilirubin, alkaline phosphatase, total protein, albumin, SGOT, HDL cholesterol or gamma glutamyl transferase were observed among the three groups, that is, the exposed workers with chloracne, the exposed workers without chloracne, and the nonexposed control workers. SGPT ($p<0.01$) and total cholesterol ($p<0.02$) were significantly higher in the exposed workers with chloracne than in exposed workers without chloracne or in the controls. Triglyceride levels were increased significantly in exposed workers without chloracne ($p<0.05$) and in exposed workers with chloracne ($p<0.01$). The effect of smoking and drinking on several of the parameters evaluated obscured the interpretation of some of the data. Eighteen months after the initial evaluation, the level of cholesterol in the blood of dichloroaniline/diuron workers was elevated (5.53 mmol/ℓ), but no concurrent controls were evaluated and no statistics were compiled. The controls from the initial study had 5.07 mmol of

cholesterol/L of blood. Triglyceride levels, however, appeared to have returned to normal 18 months after the initial study. These changes may have been the result of improved working conditions that minimized TCAB and TCAOB exposure, or of improvement in the health habits of the workers after medical consultation. An admitted weakness of this study was a lack of measured TCAB and TCAOB levels.

Blood tests and urinalysis, as well as a general health evaluation of 102 workers out of a total 111 who were employed in a carbamate pesticide manufacturing plant revealed that, in addition to the effects usually produced by cholinesterase inhibitors, 17 of 28 production workers (61%) exposed to dichloroaniline and propanil had chloracne (Morse et al., 1979). The average length of worker employment was 2 years. Morse et al. (1979) concluded that the chloracne was caused by TCAB, a contaminant of dichloroaniline and propanil.

As reported by Taylor (1979), 38% of 102 workers in an Arkansas propanil manufacturing plant had chloracne attributed to TCAB exposure. The incidence of chloracne was highest (71%) in the subgroup of production workers (Morse and Baker, 1977).

Pertinent data regarding the chronic toxicity of TCHB in either animals or humans were not located in the available literature cited in the Appendix.

5.6. OTHER RELEVANT INFORMATION

TCAB, TCAOB and TCHB are inducers of microsomal enzymes. TCAOB increased hepatic Ah-hydroxylase activity within 24 hours in chick embryos and within 48 hours in 6-week-old female C57BL/6J mice that had received an intraperitoneal injection of TCAOB (Poland et al., 1976). The ED_{50} for enzyme induction in the mice was 8200 nmol/kg bw. Both TCAB and TCAOB were reported to bind reversibly, and competitively with each other and TCDD, to

a C57BL/6J mouse liver cytosol receptor that regulates the synthesis of Ah-hydroxylase (Poland et al., 1976). Intraperitoneal injection of rats with TCAB and TCAOB increased zoxazolamine hydroxylase activity at doses of 0.05-10 mg/kg bw, doubled the amount of cytochrome P-450 that was detectable in liver homogenates at 10 mg/kg bw, but had no effect on the level of hepatic arginase, although liver weight was slightly increased (Saint-Ruf et al., 1979). Groups of three male Sprague-Dawley rats received intraperitoneal injections of 1, 10, 25 or 50 mg/kg/day of TCAB, TCAOB or TChB for 5 consecutive days (Hsia and Kreamer, 1979a). One group of three rats received corn oil only and served as the control. All three compounds induced cytochrome P-448 in a dose-dependent fashion. Maximal induction for all three compounds occurred at a dose level of 25 mg/kg/day. TCAOB was reported to be the most potent of the three and the most persistent inducer of cytochrome P-448 activity (Hsia and Kreamer, 1979b).

TCAB at a concentration as low as 0.1 mg/mℓ of culture medium had a porphyrinogenic effect in cultivated chick embryo liver cells that was ~500 times greater than the effect of hexachlorobiphenyl, a known porphyrinogenic agent (Mensink and Strik, 1982). The porphyrinogenic effect of TCAB is probably of a magnitude equal to the effect of TCDD (Strik et al., 1983; Mensink and Strik, 1982).

Sundstrom (1980) reported that an unpublished study by E.I. duPont deNemours and Company estimated the oral LD_{50} in rats as >5000 mg/kg of TCAB and the inhalation LC_{50} during a 4-hour exposure as 920 mg/m³ of TCAB. Three of 10 rabbits died with enlarged livers containing fatty degenerative changes after dermal application of 20 mg TCAB/kg/day (Sundstrom, 1980).

6. AQUATIC TOXICITY

Pertinent data regarding the toxicity of TCAB, TCAOB or TCHB to aquatic organisms were not located in the available literature cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits were not located in the available literature cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of TCAB, TCAOB or TCHB were not located in the available literature cited in the Appendix.

Hsia (1981) showed that TCAB is potentially carcinogenic based on its ability to transform mouse embryo fibroblasts *in vitro* (Hsia et al., 1977). However, no long-term *in vivo* assays assessing the carcinogenic potential of TCAB, TCAOB or TCHB were located in the literature cited in the Appendix. None of these chemicals is scheduled for testing by the National Toxicology Program (NTP, 1984).

Neither TCAB nor TCAOB was mutagenic in plate incorporation assays with *Salmonella typhimurium* strains TA98, TA100, TA1530, TA1535, TA1537, TA1538, TA1532, TA1950 (Gilbert et al., 1980); however, a marginal response to TCAB in *S. typhimurium* strain Ta1538 and TA532 for TCAB in a fluctuation test by Hsia et al. (1977). TCAB was reported to be weakly mutagenic in *Salmonella* strains, however data were not reported to substantiate this claim. Increased amounts of unscheduled DNA synthesis occurred in primary rat hepatocyte cultures treated with TCAB (Hsia and Kreamer, 1979a). Pertinent data regarding the mutagenicity of TCHB were not located in the available literature cited in the Appendix.

TCAOB at intraperitoneal doses of 6, 8 or 16 mg/kg bw is teratogenic, producing cleft palate in certain strains of mice that carry the gene for a specific cytoplasmic protein, the Ah-receptor (Hassoun et al., 1984; D'Argy et al., 1984). There is a dose-related increase in resorptions regardless of the susceptibility of a strain to cleft palate induction. TCAB and TCAOB are teratogenic to chick embryos (Schrankel et al., 1982). Pertinent data regarding the teratogenicity of TCHB were not located in the available literature cited in the Appendix.

Chronic studies regarding the toxicity of TCAB or TCAOB were not located in the available literature. Pertinent data regarding the systemic toxicity

of chronic or subchronic exposure to TCHB were not located in the available literature. A subchronic (120-day) study in rats on the effects of dietary exposure to TCAB and TCAOB has been reported (Hsia et al., 1980). The rats receiving TCAB or TCAOB in the diet at 100 ppm had consumed totals of 25.2±2.4 mg and 24.0±2.3 mg, respectively. Dividing these amounts by 120 days and by 0.35 kg (the average weight of the rats based on information provided in the report) results in equivalent dosages of 0.6 mg/kg/day for TCAB and 0.57 mg/kg/day for TCAOB. These dosages were associated with statistically significant reductions in body weight gain, hematocrit and hemoglobin concentrations and increased levels of SGOT. TCAOB, but not TCAB, treatment resulted in significant increases in liver and spleen weights and decreased red blood cell counts. The only dietary level (100 ppm) of each chemical used was associated with adverse effects; therefore, a NOAEL cannot be determined and an ADI cannot be derived.

Higher dosages of TCAB and TCAOB (25 mg/kg/day) administered intraperitoneally to rats in short-term studies result in depressed body weight gains and thymus weights, histologic changes in thymus and lymphoid tissue (Hsia et al., 1981), effects on the immune system (Hsia et al., 1982; Hinsdill et al., 1984; Olson et al., 1984), increased liver weights and hepatocytomegaly (Hsia et al., 1981; Schrankel et al., 1980).

Application of TCAB to the ears of adult female New Zealand rabbits resulted in hyperkeratosis (Hill et al., 1981) when applied daily by painting with 0.1 mL of a test solution for 5 days (total doses ranged from 0.5-32 µg). Daily application of acetone solutions of 0.1, 0.001 and 0.0001 technical grade TCAB (5 days/week) for 4 weeks resulted in comedone formation at all doses in albino rabbits (Taylor et al., 1977). An acetone control produced no comedones.

Human occupational exposure studies (see Section 5.5.) report that TCAB and TCAOB cause chloracne, but actual exposure levels were not measured. Pertinent data regarding the effects of human exposure to TCHB were not located in the available literature cited in the Appendix.

The available data for TCAB, TCAOB and TCHB are inadequate for estimation of an ADI. Although TCAOB has been found to cause cleft palate, increased fetal resorptions, hydronephrosis, and a low frequency of hydrops in mice, the i.p. method of exposure is inappropriate for human ADI derivation. Based upon the severity of these effects, however, laboratory studies utilizing an oral route of exposure are strongly suggested.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Available studies on the toxicity of TCAB and TCAOB were discussed in Chapter 5. The only study located in the available literature that is suitable for use in the derivation of RQs is the report by Hsia et al. (1980). Although the teratogenicity studies (Hassoun et al., 1984; D'Argy et al., 1984) in mice are of great significance, the intraperitoneal route of TCAOB administration precludes their use in deriving an RQ. Similarly, the 60-day study by Hsia et al. (1981) cannot be used in the derivation of RQs because the TCAB and TCAOB were administered intraperitoneally. The dietary exposure level in the Hsia et al. (1980) study was reported to be 100 ppm for both TCAB and TCAOB. The dosages in mg/kg/day can be calculated by dividing the total amount of TCAB and TCAOB consumed, 25.2±2.4 mg and 24.0±2.3 mg, respectively, by 120 days and by the body weight of the rats (reported to be ~350 g) at the midpoint of the experiment. The dosages obtained from these calculations are 0.60 mg/kg/day for TCAB and 0.57 mg/kg/day for TCAOB. By multiplying these dosages by the cube root of the animal to human body weight ratio, multiplying by the weight of an average man (70 kg), and dividing by an uncertainty factor of 10 because of the subchronic nature of the study, human MEDs of 0.72 mg/day of TCAB and 0.68 mg/day of TCAOB are obtained. The RV_d for TCAB is 5.7; the RV_d for TCAOB is 5.8. Both TCAB and TCAOB caused statistically significant decreased body weight gain, decreased hematocrit and total hemoglobin levels, and increased Ah-hydroxylase and SGOT. In addition, TCAOB caused an increase in the relative weight of the liver, spleen and testes, a decreased total red blood cell count and increased serum lipid levels. The highest RV_e that can be assigned based on the Hsia et al. (1980) feeding study is 6, based on increased levels of

SGOT, which constitutes clinical evidence of liver necrosis. Histologic examination of the liver or other tissue was not performed in this study; however, histopathologic lesions (hypertrophy, fatty degeneration) were observed in the livers of rats that were treated intraperitoneally with these chemicals (Hsia et al., 1981). Based on an RV_e of 6, the CS, a product of the RV_d and RV_e, is 34.2 for TCAB and 34.8 for TCAOB. Data used to calculate the CSs are summarized in Table 9-1. The RQ for both TCAB and TCAOB is 100 (Tables 9-2 and 9-3).

There are insufficient data to derive an RQ for TCHB (Table 9-4).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

There are no bioassay carcinogenicity data on TCAB, TCAOB and TCHB. Although their structural resemblance to TCDD and TCDF, their strong binding to the Ah-receptor protein, and the fact that TCDD is an extremely potent carcinogen aroused presumption as to their carcinogenic potential, this has not been directly tested. These chemicals would therefore be placed in EPA's group E category (no evidence of carcinogenicity); therefore, no potency factor ($F=1/ED_{10}$) can be derived for TCAB, TCAOB or TCHB.

TABLE 9-1

Composite Scores for the Toxicity of TCAB and TCAOB[a]

Compound	Species	Dose/Exposure	Chronic Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ
TCAB	rat	100 ppm in diet, 120 days (0.60 mg/kg/day)	0.72[b]	5.7	Significantly increased level of SGOT, decreased body weight gain, decreased hematologic parameters	6	34.2	100
TCAOB	rat	100 ppm in diet, 120 days (0.57 mg/kg/day)	0.68[b]	5.8	Significantly increased levels of SGOT, decreased body weight gain, increased organ weights, decreased hematologic parameters	6	34.8	100

[a]Source: Hsia et al., 1980

[b]Divided by 10 to estimate a chronic exposure level

TABLE 9-2

TCAB

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	0.72 mg/day
Effects:	significantly increased levels of SGOT, decreased body weight and decreased hematologic parameters
Reference:	Hsia et al., 1980
RV_d	5.7
RV_e	6
Composite Score:	34.2
RQ:	100

*Equivalent human dose

TABLE 9-3

TCA08

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	0.68 mg/day
Effects:	significantly increased levels of SGOT, decreased body weight, changes in organ weights and decreased hematologic parameters
Reference:	Hsia et al., 1980
RV_d	5.8
RV_e	6
Composite Score:	34.8
RQ:	100

*Equivalent human dose

TABLE 9-4

TCHB

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effects:	
Reference:	
RV_d	
RV_e	
Composite Score:	
RQ:	Data are insufficient for derving an RQ

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in November, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. United States Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.